REMARKS

Upon entry of the above Amendment, claims 1-38 will remain pending in this application. By this Amendment, claims 29, 30, and 31 have been amended to correct a typographical error. No new matter has been added.

Claim Objections

Claims 29 and 30 have been amended to correct the spelling of gabapentin in accordance with the Examiner's helpful recommendation. Claim 31 has also been amended to correct this informality. Withdrawal of this objection in light of the amendment is respectfully requested.

§ 103 Rejection of the Claims

Carter (WO 2001158881) in view of Satzinger (US 4,024,175)

Claims 1-7 and 26-31 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Carter, International Publication No. WO 2001158881, in view of Satzinger, U.S. Patent No. 4,024,175. Applicants respectfully traverse the rejection.

Applicants respectfully assert that one of skill in the art at the time the present application was filed would not have prepared a gabapentin composition using a process applying heat to sterilize the composition in light of the references cited by the Examiner, due to the known toxicity of the corresponding gabapentin lactam, the formation of which is accelerated under increased temperatures. The gabapentin lactam was known to be more than 26 times more toxic than gabapentin itself, and it was understood that a good deal of care should be taken to avoid formation of the gabapentin lactam (see, *e.g.*, US Patent No. 6,054,482 at column 4, lines 50-53). Taking the body of literature as a whole that would have been known to one of skill in the art, one would not have looked to heat treatment as an option for gabapentin compositions.

Claim 1 (and thus its dependent claims 2-7 and 26-31) recites heating an injectable composition comprising gabapentin.

Nothing in the Carter publication or the Satzinger patent, either alone or in combination, would have lead one of skill in the art to prepare an injectable gabapentin formulation using a

process involving heat-treatment for sterilization of the composition. As identified in the Office Action, Carter teaches that:

(i) certain pyrimidine derivatives may be selective inhibitors of COX-2 and may be of use in the treatment of, *inter alia*, epilepsy (page 8, lines 1-2);

(ii) such pyrimidine derivatives may be presented with conventional carriers or excipients (page 10, line 25-27) and may be formulated in any suitable manner, including for parental administration (page 10, lines 28-31), which may be given as an injection or continuous infusion (e.g., intravenously, intravascularly or subcutaneously) (page 11, lines 7-11);

(iii) such pyrimidine derivatives may be made into an injectable solution that may be packaged in, *e.g.*, ampoules, vials or syringes and that the "ampoules, vials or syringes may be aseptically filled (e.g. the solution may be sterilized by filtration and filled into sterile ampoules under aseptic condictions) and/or terminally sterilized (e.g. by heating in an autoclave using one of the acceptable cycles)" (page 28, lines 1-5);

(iv) such injectable solution is preferably filled into ampoules and terminally sterilized (page 28, lines 6-7);

(v) such pyrimidine derivatives may be used in conjunction with other therapeutic agents, including gabapentin (page 9, line 26-28 and page 10, line 3); and

(vi) such pyrimidine derivatives and the other therapeutic agents (such as gabapentin) may be combined in a formulation (page 11, line 28-page 12, line 2).

However, Carter does not specifically teach that a composition comprising gabapentin may be heat-treated. In fact, Carter does not discuss whether compounds that are known to produce toxic decomposition products would be suitable for admixture with such pyrimidine derivatives in a terminally sterilized injectable composition.

Carter lays out a vast multitude of potential formulation choices that may be taken with regard to COX-2 inhibiting pyrimidine derivatives and additional therapeutic agents. For example, Carter discloses:

(i) about 50 broad classes or subclasses of compounds and about 30 different specific compounds , only one of which is gabapentin, that may be used in combination

with a COX-2 inhibiting pyrimidine derivative (page 9, line 26 – page 10, line 19);

(ii) that any suitable formulation preparation may be used including topical, inhalation, oral, transdermal, or parental (page 10, line 28-34), and that, e.g., for oral delivery the formulations may be a tablet, capsule, powder, solution, syrup or suspension (p. 11, lines 1-4); and

(iii) that the additional therapeutic agents may be prepared in the same formulation as the pyrimidine derivates or may be in a separate formulation (page 11, line 28 – page 12, line 2).

Carter lays out a bewildering array of choices for formulating COX-2 inhibiting pyrimidine derivatives with (or without) additional therapeutic agents. Based on the choices presented in the Carter reference, Applicants assert that one of skill in the art would not have been lead to a heat-treated sterilized injectable composition comprising gabapentin in light of the known toxicity of the gabapentin lactam.

Satzinger does not overcome the deficiencies of Carter. The Satzinger patent is the underlying gabapentin patent that described for the first time the synthesis of gabapentin and related cyclic amino acids and their potential usefulness in treating certain diseases, including epilepsy. While the Satzinger patent disclosed that gabapentin may be formulated in an injectable formulation in individual dosage amounts of between 5 and 50 mg (column 3, lines 24-52), the patent did not disclose that such injectable formulations may be heat-treated for sterilization. In addition, the Satzinger patent did not discuss, and apparently did not even recognize, the toxicity issues related to the gabapentin lactam. Later publications revealed the starkly increased toxicity of the lactam relative to gabapentin (see, *e.g.*, US Patent No. 6,054, 482, which states at column 4, lines 50-53 that gabapentin has a toxicity (LD_{50}, mouse) of more than 8000 mg/kg, while the corresponding lactam has a toxicity of 300 mg/kg.) At the time the present application was filed, one of skill in the art was well aware of the toxicity issues presented by the gabapentin lactam, and would not have chosen a process for preparing an injectable gabapentin composition that included heat-treatment based on the teachings of Carter and Satzinger.

Applicants have shown that heat-treated and sterilized gabapentin compositions are effective and surprisingly safe when delivered intrathecally to rats (see paragraphs 55-68 and the

discussion presented at paragraph 70 of the present application). In light of the known toxicity of the gabapentin lactam and the increased degradation of gabapentin to the lactam due to heating, Applicants assert that one of skill in the art would have been steered away from heat-treating injectable compositions of gabapentin upon reading the Carter and Satzinger references. It was not until Applicants surprising results presented in the present application that heat-treatment of gabapentin was shown to be a safe and effective process for preparation of injectable gabapentin compositions.

Nothing in the Carter and Satzinger references, either alone or in combination, would have lead one of skill in the art to a process as in claim 1 (and thus its dependent claims 2-7 and 26-31). Withdrawal of the rejection is respectfully requested.

Carter (WO 2001158881) in view of Satzinger (US 4,024,175), Aikus (US 5,603,894), and Grote (US 6,046,353)

Claims 8-20 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Carter, International Publication No. WO 2001158881, in view of Satzinger, U.S. Patent No. 4,024,175, and further in view of Aikus, U.S. Patent No. 5,603,894, and in further view of Grote, U.S. Patent No. 6,046,353. Applicants respectfully traverse the rejection.

As stated above regarding claims 1-7 and 26-31, one of skill in the art would not have been lead to preparing an injectable gabapentin composition prepared by a process including heat-treatment for sterilization based on the Carter publication and the Satzinger patent, due to the known toxicity of the gabapentin lactam, whose production would be accelerated by heat-treatment. This holds true for claims 8 (and its dependent claims 9-12) and claim 13 (and its dependent claims 14-20), which recite degrees of heating even greater than required by claim 1. For example claim 8 recites heating the injectable gabapentin composition at greater or equal to about 105°C for greater than or equal to about 2 minutes, and claim 13 recites heating the injectable gabapentin composition to an F_0 of about 1 or greater. The Aikus and Grote patents, either alone or in combination, do not overcome the deficiencies of the combination of the Carter publication and the Satzinger patent.

The Aikus patent and the Satzinger patent teach that it is prudent to minimize the exposure of heat-sensitive compounds to heat. According to the Office Action, the Aikus patent discloses that the temperature and time required to obtain a particular degree of sterilization may

be calculated and adjusted to minimize thermal degradation of a heat-sensitive compound. The Aikus patent appears to be concerned with yield, *i.e.* the loss of parent compound due to thermal decomposition (see, e.g., column 1, lines 28-30, stating "the higher the temperature, the more the composition degrades", and "the longer the composition is exposed to heat, the more the composition degrades"), rather than the generation of toxic decomposition products. While Aikus may teach that it can be possible to reduce thermal decomposition while achieving a certain level of sterilization, the methods taught by Aikus would still result in increased degradation relative to a process that did not involve heat-treatment. Applicants assert that one of skill in the art would not have chosen to employ a method that would result in an increased level the gabapentin lactam (even though somewhat minimized) if one knew that the decomposition product had a toxicity level of more than 26 times that of the parent compound. That is, if one had the choice between a procedure for producing an injectable composition that included a degradation product having more than 26 times the toxicity of the parent compound, one would not be inclined to choose a process that involved heat-treatment, regardless of whether production of the degradation product could be slightly reduced.

The Grote patent does nothing to cure the deficiencies of the combined teachings of the Carter publication, the Satzinger patent and the Aikus patent – in fact the Grote patent appears to teach away from heat-treatment as part of a process to sterilize heat sensitive compounds. The Grote patent teaches that heating and temperature should be kept to a minimum to prevent decomposition of racemic 3-aminomethyl-5-methylhexanoic acid to the corresponding lactam so that product yield is not lowered (column 16, lines 5-9). However, Grote teaches that the batch should be heated to 50-65°C, just long enough to dissolve the solids (column, 16, lines 3-4). Grote clearly suggests that any unnecessary heating should be avoided to prevent loss of yield due to lactam formation. That is, Grote teaches away from heat-treatment as part of a sterilization procedure. If the lactam produced by the process discussed above with regard to Grote resulted in a lactam having a toxicity level more than 26 times greater than the corresponding 3-aminomethyl-5-methylhexanoic acid (as is the case for the gabapentin lactam), Grote could only be construed to teach even further away from use of any heat-treatment as a part of the sterilization process.

When presented with a choice to heat treat or not to heat treat as part of a sterilization process, one may be arguably inclined to heat treat if one were merely going to achieve lower

yield at the expense of the production of a decomposition product (but not according to the Grote patent, as discussed above). But, if that decomposition product is known to be more than 26 times more toxic than the corresponding parent compound, one would choose an option other than heat-treatment. Nothing in the combined teachings of the Carter publication, the Satzinger patent, the Aikus patent or the Grote patent teaches otherwise. In fact, the Grote patent appears to emphasize this point. This is particularly the case with the degrees of heating recited in claims 8-20 of the present application. Accordingly, withdrawal of the rejection is respectfully requested.

Carter (WO 2001158881) in view of Satzinger (US 4,024,175) and Augart (US 6,054,482)

Claims 21-25 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Carter, International Publication No. WO 2001158881, in view of Satzinger, U.S. Patent No. 4,024,175, and further in view of Augart, U.S. Patent No. 6,054,482. Applicants respectfully traverse the rejection.

As stated above with regard to claim 1, one of skill in the art would not have been lead to preparing an injectable gabapentin composition prepared by a process including heat-treatment for sterilization based on the Carter publication and the Satzinger patent, due to the known toxicity of the gabapentin lactam, whose production would be accelerated by heat-treatment. Claims 21-25 depend, either directly or indirectly from claim 1. Accordingly, the deficiencies in the combined teachings of the Carter publication and the Satinger patent as applied to claim 1 are also deficiencies as applied to claims 21-25. The Augart patent does not overcome the deficiencies of the combination of the Carter publication and the Satzinger patent.

The Augart patent does nothing to cure the deficiencies of the combined teachings of the Carter publication and the Satzinger patent, and, in fact emphasizes these deficiencies. The Aguart patent at column 4, lines 50-57 states that the gabapentin lactam has a toxicity more than 26 times greater than gabapentin, that such decomposition products (the lactams) "*must* be reduced to a minimum for reasons of safety" (emphasis added). As stated above for the rejection based on the combination of Carter in view of Satzinger, Aikus, and Grote, if one were to choose between a process that involved heat-treatment for a composition comprising gabapentin versus a process that did not involve heat-treatment, one would choose the process that did not involve heat-treatment due to the known toxicity of the gabapentin lactam. This assertion is clearly

supported by the disclosure of the Aguart patent. Accordingly, withdrawal of the rejection is respectfully requested.

Carter (WO 2001158881) in view of Satzinger (US 4,024,175) and Kulkarni (US 2002/0198261)

Claims 21-25 and 32-35 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Carter, International Publication No. WO 2001158881, in view of Satzinger, U.S. Patent No. 4,024,175, and further in view of Kulkarni, U.S. Pre-Grant Patent Application Publication No. 2002/0198261. Applicants respectfully traverse the rejection.

As stated above with regard to claim 1, one of skill in the art would not have been lead to preparing an injectable gabapentin composition prepared by a process including heat-treatment for sterilization based on the Carter publication and the Satzinger patent, due to the known toxicity of the gabapentin lactam, whose production would be accelerated by heat-treatment. Claims 21-25 and 32 depend, either directly or indirectly from claim 1. Accordingly, the deficiencies in the combined teachings of the Carter publication and the Satinger patent as applied to claim 1 are also deficiencies as applied to claims 21-25 and 32. Claim 33, and thus its dependent claims 33-35, recite heating a container housing an injectable gabapentin formulation, and the deficiencies in the combined teachings of the Carter publication and the Satinger patent as applied to claim 1 are also applicable to claims 33-35.

The Kulkarni publication does nothing to cure the deficiencies of the combined teachings of the Carter publication and the Satzinger patent, and, in fact emphasizes these deficiencies. The Kulkarni publication states that levels of the gabapentin lactam "must be reduced for safety reasons" and that "liquid formulations of gabapentin undergo cyclization to form lactam much more readily than in the solid state" (paragraph 10), and that this (at least in part) lead to the decision to limit pharmaceutical compositions of gabapentin to solid dosage forms (paragraph 11). Clearly, the teachings of Kulkarni would lead one away from a process that would involve heat treatment as part of sterilization for a gapapenting composition, especially an injectable gabapentin composition. Accordingly, withdrawal of the rejection is respectfully requested.

Carter (WO 2001158881) in view of Satzinger (US 4,024,175), Kulkarni (US 2002/0198261), and Aikus (US 5,603,894)

Claims 36-38 have been rejected under 35 U.S.C. § 103(a) as being unpatentable by Carter, International Publication No. WO 2001158881, in view of Satzinger, U.S. Patent No. 4,024,175, and further in view of Kulkarni, U.S. Pre-Grant Patent Application Publication No. 2002/0198261, and in further view of Aikus, U.S. Patent No. 5,603,894, and in further view of Grote, U.S. Patent No. 6,046,353 Applicant respectfully traverses the rejection.

As stated above with regard to claim 33-35, one of skill in the art would not have been lead to preparing an injectable gabapentin composition prepared by a process including heat-treatment for sterilization based on combined teachings of the Carter publication, the Satzinger patent and the Kulkarni publication, but rather would be lead away from such a process based on the combined teachings of these publications and patents. Claims 36-38 depend from claim 33. Accordingly, the deficiencies in the combined teachings of combined teachings of the Carter publication, the Satzinger patent and the Kulkarni publication as applied to claim 33 are also deficiencies as applied to claims 36-38. However, such deficiencies are enhanced because the degrees of heating recited by claims 36-38 are even greater than required by claim 33.

The Aikus patent does nothing to cure the deficiencies of the combined teachings of the Carter publication, the Satzinger patent and the Kulkarni publication. According to the Office Action, the Aikus patent discloses that the temperature and time required to obtain a particular degree of sterilization may be calculated and adjusted to minimize thermal degradation of a heat-sensitive compound. The Aikus patent appears to be concerned with yield, *i.e.* the loss of parent compound due to thermal decomposition (see, e.g., column 1, lines 28-30, stating "the higher the temperature, the more the composition degrades", and "the longer the composition is exposed to heat, the more the composition degrades"), rather than the generation of toxic decomposition products. While Aikus may teach that it can be possible to reduce thermal decomposition while achieving a certain level of sterilization, the methods taught by Aikus would still result in increased degradation relative to a process that did not involve heat-treatment. Applicants assert that one of skill in the art would not have chosen to employ a method that would result in an increased level the gabapentin lactam (even though somewhat minimized) if one knew that the decomposition product had a toxicity level of more than 26 times that of the parent compound. That is, if one had the choice between a procedure for producing an injectable composition that

included a degradation product having more than 26 times the toxicity of the parent compound, one would not be inclined to choose a process that involved heat-treatment, regardless of whether production of the degradation product could be slightly reduced. As the Aikus patent does not cure the deficiencies in the combined teachings of the Carter publication, the Satzinger patent and the Kulkarni publication, withdrawal of the rejection is respectfully requested.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of the merits of the present application and earnestly solicit notification of allowance of all the claims.

The Examiner is respectfully requested to contact the undersigned by telephone at 763.505.0405 or by E-mail at keith.m.campbell@medtronic.com with any questions or comments.

Please grant any extension of time, if necessary for entry of this paper, and charge any fee due for such extension or any other fee required in connection with this paper to Deposit Account No. 13-2546.

Respectfully submitted,

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